☐ 1: Trends Mol Med 2002;8(4 Suppl):S55-61

Links

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Hsp90 inhibitors as novel cancer chemotherapeutic agents.

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Heat shock protein 90 (Hsp90) is a molecular chaperone whose association is required for the stability and function of multiple mutated, chimeric and over-expressed signaling proteins that promote the growth and/or survival of cancer cells. Hsp90 client proteins include mutated p53, Bcr-Abl, Raf-1, Akt, ErbB2 and hypoxia-inducible factor 1 alpha (HIF-1 alpha). Hsp90 inhibitors, by interacting specifically with a single molecular target, cause the destabilization and eventual degradation of Hsp90 client proteins, and they have shown promising antitumor activity in preclinical model systems. One Hsp90 inhibitor, 17-allylaminogeldanamycin (17AAG), is currently in phase I clinical trial. Because of the chemoprotective activity of several proteins that are Hsp90 clients, the combination of an Hsp90 inhibitor with a standard chemotherapeutic agent could dramatically increase the in vivo efficacy of the therapeutic agent.

Publication Types:
- Review
- Review, Tutorial

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1: Leukemia 2002 Apr;16(4):455-62

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Hsp-90-associated oncoproteins: multiple targets of geldanamycin and its analogs.

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Geldanamycin (GA), herbimycin A and radicicol bind heat-shock protein-90 (Hsp90) and destabilize its client proteins including v-Src, Bcr-Abl, Raf-1, ErbB2, some growth factor receptors and steroid receptors. Thus, Hsp90-active agents induce ubiquitination and proteasomal degradation of numerous oncoproteins. Depending on the cellular context, HSP90-active agents cause growth arrest, differentiation and apoptosis, or can prevent apoptosis. HSP-active agents are undergoing clinical trials. Like targets of most chemotherapeutics, Hsp90 is not a cancer-specific protein. By attacking a nonspecific target, HSP-90-active compounds still may preferentially kill certain tumor cells. How can this be achieved? How can therapeutic potentials be exploited? This article starts the discussion.

Publication Types:
- Review
- Review, Academic

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